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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,469	12/22/2000	Kyogo Itoh	0020-4792P	2449

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EXAMINER	
DAVIS, NATALIE A	

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 06/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/720,469	Applicant(s) ITOH ET AL.	
	Examiner Natalie A. Davis	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *9-11 and 15-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-14 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's traversal of the election of Group I, claims 1-14 and 25, SEQ ID NO: 2 is acknowledged. The traversal is on the ground(s) that the Groups I-V are linked, the special technical feature of linking the invention is cyclophilin-derived peptides, and a copy of the Shichijo reference was not provided. This is not found persuasive for reasons indicated in the previous office action, Groups I-V are not linked by a special technical feature, which defines a contribution over the prior art, in this case antigeneic peptides recognized by CTL. A copy of the Shichijo was not provided, since it was disclosed in the information disclosure statement submitted by applicant, however a copy will be provided for your consideration.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-8, 12-14 and 25 as it reads on SEQ ID NO: 2 are being examined as belonging to the elected Group I, while claims 9-11 and 15-24 are withdrawn from examination as being drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure statement has been considered. A signed copy is attached hereto.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-8, 12-14, and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite a "tumor antigen peptide that is a partial peptide." This is indefinite as it is not clear what other peptide the tumor antigen comprises other than the peptide derived from cyclophilin.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8, 12-14, and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The nature of the invention is a tumor antigen peptide. The specification defines a tumor antigen peptide as a partial peptide comprising part of cyclophilin B and is capable of binding to an HLA antigen and is recognized by CTL. Likewise, any peptide falls within the scope of being a tumor antigen peptide as long as it comprises a part of the amino acid sequence of human cyclophilin B, Accession number M60857 and a complex between said peptide and an HLA antigen is capable of being recognized by CTL (p. 11). The invention is further drawn a derivative of a partial peptide derived from cyclophilin. There are many peptides that may or may not bind to an HLA antigen and is recognized by CTL, which may be derived from cyclophilin. The specification defines a derivative as any altered peptide which contains alterations of one or more amino acid residues (p. 17), but the specification does not give any guidance to which amino acids of cyclophilin will exhibit the biological activities as the claimed, or any guidance as to which regions of amino acid sequence are responsible for biological activity and thus, must be preserved so the molecule will function as claimed. Thus, it would be an undue burden to one of ordinary skill in the art to assay for said derivative sequences, which are capable of functioning as contemplated. One cannot extrapolate the teachings of the specification to the breadth of the claims because the claims are broadly drawn to any derivative

of cyclophilin and applicant has not enabled all of these types of modifications because it has not been shown that these peptides are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the breadth of the claims and the enablement set forth, and it cannot be predicted from the disclosure as to which cyclopilin derivatives or derivatives thereof will function as contemplated. Therefore, in view of the lack of predictability of the prior art, lack of working examples, the breadth of the claims, and insufficient guidance as indicated above, one of skill in the art would not be able to practice the claimed invention because undue experimentation would be required.

5. Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is prevention of tumors using tumor antigen peptides derived from cyclophilin B. The specification discloses the identification of tumor antigen peptides (p. 39 and 49) and the induction of CTL from peripherial blood lymphocytes by cyclophilin protein (p. 59), but here are no working examples describing how the invention may be used to prevent tumors. There are no working examples or guidance asserting the prevention of any tumors using pharmaceutical compositions wherein the active ingredient is a tumor antigen peptide of cyclophilin or a derivative thereof. Likewise, there is no evidence in the art teaching the prevention of tumors. Therefore, in view of the lack of working examples, it would be unpredictable and would require undue experimentation to one skilled in the art to practice the invention as claimed.

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Claims 1-8, 12-14, and 25 are rejected under 35 U.S.C. 112, first paragraph. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Vas-Cath Inc. v. Mahurkar (CA FC) 19 USPQ2d 1111 (6/7/1991) clearly states that "written description" of invention required by first paragraph of 35 U.S.C. 112 is separate and distinct from that paragraph's requirement of enabling disclosure, since description must do more than merely provide explanation of how to "make and use" invention; applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed. An applicant shows possession by describing the claimed invention with all it limitations using such descriptive means as words, structures, diagrams, and formulas. Also, description of an actual reduction to practice, or by showing the invention was "ready for patenting," or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention at the time of filing.

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The nature of the invention is a derivative of a tumor antigen peptide. The specification does not reasonably provide written description for derivatives of a tumor antigen peptide

derived from cyclophilin B. The specification discloses derivative as any altered peptide, which contains alterations of one or more amino acid residues, but does not disclose the isolation of and assaying of said derivative or genes encoding cyclophilin B. There is no actual reduction to practice, sufficient descriptive information, such as definitive structural features, which are critical to polypeptide activity, or complete detailed description of the function of claimed invention indicating that the claimed derivatives or genes encoding cyclophilin B were indeed isolated, produced, and assayed for the uses disclosed. Thus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-8, 12-14, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Price, et al. (1991).

Price teach the amino acid sequence of human cyclophilin B. Price anticipates the invention as claimed since the specification defines a tumor antigen peptide as a partial peptide comprising part of cyclophilin B, any peptide, regardless of length, as long as it comprises a part of the amino acid sequence of human cyclophilin B, Accession number M60857 (p. 11), or any derivative which contains alterations of one or more amino acid residues (p. 17). It is inherent that the tumor antigen peptide taught by Price is capable of binding to an HLA antigen, is recognized by CTL, is capable of treating a tumor and diagnosing tumors, since it comprises the cyclophilin B amino acid sequence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Natalie A. Davis whose telephone number is 703-308-6410. The examiner can normally be reached on M-F 8-5:30 (every other Friday off).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa PhD can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4315 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Natalie A. Davis PhD
June 11, 2002

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